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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,067	12/16/2004	Carlo Bertucci	P27,959 USA	3245

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EXAMINER	
LAM, ANN Y	
ART UNIT	**PAPER NUMBER**
1641	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,067	BERTUCCI ET AL.	
	Examiner	Art Unit	
	Ann Y. Lam	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-27* is/are rejected.

7)☒ Claim(s) *13,14,17, 18,25 and 27* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/11/06, 1/27/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Specification

The disclosure is objected to because of the following informalities: there does not appear to be an abstract.

Appropriate correction is required.

Claim Objections

Claims 13, 14, 17, 18, 25 and 27 are objected to because of the following informalities:

"immobilised" should be –immobilized—(in claim 13, line 2, claim 14, line 2, claim 18, line 4, claim 25, line 2, and claim 27, line 2); and

"favour" should be –favor—(in claim 18, line 5);

"(e.g., donepezil hydrochloride, sold under the trade name Asicept)" in claim 17, line 6, should be deleted because the suggested deletion of the example and the tradename would clarify the scope of the claim.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 24 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 24 recites "substantially as described herein with reference to the examples". It is not clear which examples and what elements of such examples are intended to be part of the claim. For examination purposes, claim 24 is interpreted as if it is claim 12.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 12-21, 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sunshine et al., 4,868,214, in view of Voet et al., Fundamentals of Biochemistry, 1999, John Wiley & Sons, Inc., pages 103-104.

As to claim 12, Applicants claim a method for selecting an enantiomer of a chiral compound by exposing a mixture of enantiomers to serum albumin and separating the unbound enantiomer from the albumin. The invention is substantially disclosed by Sunshine et al. because Sunshine et al. teach that the S(+)ketoprofen can be obtained free of R(-)ketoprofen through various means (col. 8, line 55 – col. 9, line 68) and the S(+)ketoprofen can be advantageiously administered to mammals suffering from pain (col. 4, lines 30-32 and 50-51, as this enantiomer elicits enhanced analgesic response in mammalian organism (col. 1, lines 12-17). Sunshine et al. also disclose that others have investigated the binding properties of the + and – enantiomers of ketoprofen to human serum albumin and have found stereoselectivity in binding to human serum albumin (col. 2, line 66 – col. 3, line 9). While Sunshine et al. disclose the various techniques for preparing S(+)ketoprofen and also disclose that HPLC (high performance liquid chromatography) methods for resolving enantiomers of other compounds are likely adaptable to resolution of ketoprofen (col. 9, liens 19-22), Sunshine et al. do not specifically teach utilizing albumin to select an enantiomer.

However, Voet et al. teach in the Fundamentals of Biochemistry textbook on pages 103-104 that affinity chromatography is a technique in which a molecule (a ligand) that specifically binds to the protein of interest is covalently attached to an inert matrix and when an impure protein solution is passed through this chromatographic material, the desired protein binds to the immobilized ligand, whereas other substances are washed through the column with buffer. Voet et al. teach that the desired protein can then be recovered in highly purified form by changing the elution conditions to

release the protein from the matrix. Voet et al. teach that the great advantage of affinity chromatography is its ability to exploit the desired protein's unique biochemical properties rather than the small differences in physicochemical properties between proteins used by other chromatographic methods.

Given that Sunshine et al. disclose that + and – enantiomers of ketoprofen binding to human serum albumin have been found to be stereoselective and that it is desirable to obtain the + enantiomers of ketoprofen, free of the – enantiomers for therapeutic purposes, and that various means may be utilized to obtain the + enantiomers, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize affinity chromatography as generally taught by Voet et al. using albumin to selective for the desired enantiomer because Voet et al. teach that affinity chromatography is an advantageous technique for recovering a highly purified form of a substance. That is, given that Sunshine et al. disclose that the binding of enantiomers of ketoprofen to albumin is stereoselective and that various means can be utilized to obtain the desired + enantiomer to be used for therapeutic purposes, it would have been obvious to utilize affinity chromatography as generally taught by Voet et al. using the appropriate binding partner that binds to one enantiomer but not the other because this technique provides the advantage of recovering a highly purified form of the desired substance, in this case the + enantiomer. While Sunshine et al. do not disclose which enantiomer binds to the albumin, such discovery is within the skills of the ordinary artisan, as Voet et al. teach that in utilizing affinity chromatography, the binding separates the materials, and the nonbound material can be eluted and where the

desired material is bound to the column, the desired bound material can be subsequently eluted also.

As to claim 13, given the teachings of Voet et al. of immobilizing the ligand which will bind to the material of interest, one would bind the albumin. (The albumin is considered to be highly homogenous because Applicants have not provided disclosure or definition such that the albumin disclosed by Sunshine et al. would not be considered highly homogenous.)

As to claim 14, the column is considered to be enantioselective because Sunshine et al. disclose that the binding of the enantiomers of ketoprofen is stereoselective.

As to claim 15, the step of separating the bound enantiomer from albumin is taught by Voet et al. on page 103, in order to recover it in highly purified form.

As to claim 16, the chiral compound is a profen (i.e., ketoprofen, disclosed by Sunshine et al.)

As to claim 17, the chiral comound is ketoprofen (disclosed by Sunshine et al.)

As to claim 18, affinity chromatography technique discussed above regarding claim 12 is a method for increasing the purify of an agent, in this case, an enantiomer of ketoprofen, and the steps of removing unbound and eluting the agent is disclosed by Voet et al. as discussed above.

As to claim 19, the step of formulating a separated enantiomer with increased purity with a pharmaceutically acceptable carrier or diluent to produce a pharmaceutical

preparation is disclosed by Sunshine et al. (see col. 4, lines 50-51 and col. 7, lines 36-41.)

As to claim 20, the step of presenting the pharmaceutical preparation in a unit dosage form is disclosed by Sunshine et al. (see col. 5, lines 32-35).

As to claim 21, in the combination of the references, the albumin is human serum albumin (see Sunshine et al. col. 2, line 68) and it is considered to be highly homogenous because Applicants have not provided disclosure or definition such that the albumin disclosed by Sunshine et al. would not be considered highly homogenous.

As to claim 23, the enantiomer in the combination of the teachings of the references is an enantiomer of a chiral compound (ketoprofen, disclosed by Sunshine et al.).

As to claim 24, the method is disclosed as discussed in claim 12. (Claim 24 is vague for the reasons set forth above and thus is interpreted to be the method of claim 12.)

As to claim 25, in the combination of the references, the column comprising an immobilized serum albumin (see discussion of claim 12) and as noted earlier, it is considered to be highly homogenous.

As to claim 26, the affinity chromatography disclosed by Voet et al. is considered to be an HPLC (i.e., high performance liquid chromatography) because the albumin is immobilized for binding to specific substances while other substances are washed through the column with buffer.

Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sunshine et al., 4,868,214, in view of Voet et al., Fundamentals of Biochemistry, 1999, John Wiley & Sons, Inc., pages 103-104, as applied to claim 12 above, and further in view of Ohmura et al., 5,21,287.

Sunshine et al. in view of Voet et al. disclose the invention substantially as claimed (see above regarding claim 12), except for the serum albumin being recombinant serum albumin.

However, Ohmura et al. teach that obtaining human serum albumin from blood has disadvantages such as not being economical and the supply of blood being sporadic and sometimes having undesirable substances such as hepatitis virus, which is avoided by recombinant technology to produce serum albumin (col. 1, lines 36-51) and Ohmura et al. further disclose such recombinant techniques (col. 4, lines 10-38). It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize recombinant technology as taught by Ohmura et al. to produce the serum albumin for the Sunshine et al. in view of Voet et al. method because Ohmura et al. teach that recombinant technology avoids the disadvantages of obtaining serum albumin from blood. (Such recombinant technique results in recombinant serum albumin and it is considered to be highly homogenous because Applicants have not provided disclosure or definition such that the albumin disclosed by Sunshine et al. would not be considered highly homogenous.)

Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sunshine et al., 4,868,214, in view of Voet et al., Fundamentals of Biochemistry, 1999, John Wiley & Sons, Inc., pages 103-104, as applied to claims 12-14, and further in view of Jain et al., 5,153,166.

Sunshine et al. in view of Voet et al. disclose the invention substantially as claimed (see claims 12-14 above), except for the column comprising the albumin immobilized on a silica matrix.

However Jain et al. teach that important advantages accruing from the use of silica supports in affinity chromatography have been found, including high accessible capacity, complete resistance to microbial attach, ease and versatility of immobilization chemistry, high purification efficiency and excellent flow properties (col. 3, lines 17-22).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to provide silica (considered to be silica matrix) taught by Jain et al. as the specific solid resin matrix disclosed by Voet et al. (see Figure 5-7 on page 103), because Jain et al. teach that silica provides the important advantages including high accessible capacity, complete resistance to microbial attach, ease and versatility of immobilization chemistry, high purification efficiency and excellent flow properties.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ann Y. Lam whose telephone number is 571-272-0822. The examiner can normally be reached on Mon.-Fri. 10-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ANN YEN LAM
PATENT EXAMINER